phase separation due to differentiated cell-cell adhesion. Various nontrivial emerging patterns resembling observed tumor morphology were identified over the parameter space of our model. However, the previous development and analysis of our model have been implicitly based on the assumption of a homogeneous microenvironmental background and unrestricted boundaries. Most clinically relevant tumors are constrained by particular organ tissue structures that may co-evolve with the progressing tumors and have profound impact on tumor-microenvironment interactions. Here we adopt a recently developed diffuse-domain approach, utilizing the Cahn-Hilliard equation framework we have previously established, to adapt partial-differential-equation models of tumor growth to a co-evolving tissue geometry. We will demonstrate this approach by modeling the growth of lymphoma within a lymph node and ductal carcinoma in situ within mammary ducts.

2540-Pos Board B559
Biochemical Response and the Effects of Bariatric Surgeries on Type 2 Diabetes
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A general method is introduced for calculating the biochemical response to pharmaceuticals, surgeries, or other medical interventions. This method is then applied in a simple model of the response to Roux-en-Y-gastric bypass (RYGB) surgery and related procedures. We specifically address the amazing fact that glucose homeostasis is usually achieved immediately after RYGB surgery, long before there is any appreciable weight loss. This result is usually attributed to a dramatic increase in an incretin, glucagon-like peptide 1 (GLP-1), but our model indicates that this mechanism alone is not sufficient to explain the largest declines in glucose levels or measured values of the homeostatic model assessment insulin resistance (HOMA-IR). The most robust additional mechanism would be production of a substance which opens an insulin-independent pathway for glucose transport into cells, analogous to the established insulin-independent pathway associated with exercise.

2541-Pos Board B560
Modeling Cluster Formation by Multivalent Interacting Proteins: Nephrin-Nck-NWasp Signaling in the Foot Process of Kidney Podocytes
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Intracellular function is often defined by clusters consisting of multiple multivalent molecules. Studying these clusters represents a significant challenge because of the potentially infinite number of cluster compositions and the intermediate complexes that are formed while clusters are formed. To make the matter worse, many clusters are very liquid, the affinities of the many bimolecular site interactions are quite modest, implying that off-rates are relatively rapid. Thus, we need efficient methods to predict the average composition of these ensembles, characterizing number of molecules of different types, number of bonds per different molecule types, and other parameters defining the size and structure of the cluster. Here we present a stochastic steady state algorithm for multivalent interacting molecules to determine cluster compositions and sizes based on probability that each type of binding site is bound. The advantage of the method is in its efficiency: tracking the formation of the cluster over time would require computation of binding and unbinding steps; instead, we identify a distribution of cluster compositions at the time point of interest based on the pairwise binding probability among multiple sites within interacting molecules. The method is applied to the system Nephrin-Nck-NWasp. The interaction between these three multi-domain molecules is required for maintenance of the podocyte foot processes cytoskeleton, the key cellular structure in the kidney slit diaphragm filtration system. The weak individual site pair affinities and estimated nephrin concentrations at the slit diaphragm by themselves would be insufficient to promote actin polymerization. We use our method to address how the multi domain and cooperative mechanisms could provide such function. Supported by NIH grants TR01DK087650 and P41GM103313.

Synaptic Transmission

2542-Pos Board B561
Synaptic Vesicle Capture by Intact CaV2.2 Channels
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The fusion of synaptic vesicles (SVs) at the presynaptic transmitter release face is gated by Ca^{2+} influx from nearby voltage gated calcium channels (CaV). Our early functional studies argued that the CaV and SV are linked by a molecular anchor or 'tether' and recent studies have proposed a direct cytoplasmic link to the channel distal C terminal. In order to explore CaV-SV binding we developed an in vitro assay, termed SV-PD, to test for capture of purified, intact SVs. Antibody-immobilized presynaptic or expressed CaV2.2 channels but not plain beads, IgG or pre-blocked antibody successfully captured SVs, as assessed by Western blot for a variety of protein markers. SV-PD was also observed with a distal C terminal fusion protein, C3strep, supporting involvement of this CaV region. Our results favor the model where presynaptic CaV can tether SVs directly, independently of the surface membrane.

2543-Pos Board B562
Optical Modulation of Neurotransmission
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The computational properties of an isolated neuron have been analyzed in detail by postsynaptic activation with caged compounds. However, new tools are needed to manipulate neurotransmission at individual synapses in order to understand how a neuron integrates physiological stimuli received from presynaptic neurons within a circuit. Here we describe a method to control neurotransmitter exocytosis at the presynaptic compartment by using a light-gated glutamate receptor (LiGluR). In chromaffin cells, LiGluR supports exocytosis by means of a calcium influx that is comparable to voltage-gated calcium channels. Presynaptic expression of LiGluR in hippocampal neurons enables direct and reversible control of neurotransmission with light, and allows modulating the firing rate of the postsynaptic neuron with the wavelength of illumination. This method constitutes an important step toward the determination of the complex transfer function of individual synapses.

2544-Pos Board B563
Molecular Mechanisms of Synchronous Synaptic Transmission
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Complexin and Synaptotagmin work in concert to couple the SNARE-mediated membrane fusion machinery to the triggering signal i.e. influx of Ca^{2+} ions. The SNARE assembly process is arrested at a very late stage by Complexin, to prevent spontaneous fusion events and the Complexin clamp is reversed by Synaptotagmin in a Ca^{2+}-dependent manner to synchronize the neurotransmitter release. To understand the mechanistic details of this process, we developed a Nanodisc based system, which allows us to generate trans-SNARE complexes under soluble conditions. SNAREs on Nanodisc assemble but do not fuse due to the topological constraints placed by the Nanodiscs. We employed a VAMP construct (VAMP-4X) which carries mutations in the C-terminal hydrophobic layers that prevent assembly of this region with the t-SNARE to accurately recreate the pre-fusion SNARE complex between two bilayers that mimic the vesicle-bilayer junction in docked vesicles. Fluorescence analysis show that the Synaptotagmin binds to the pre-fusion SNAREpin between the two bilayer under Ca^{2+} free conditions and the primary interaction is such that SNARE assembly or Complexin binding does not affect it. Calcium- additions triggers a very rapid co-penetration of the Ca^{2+}-binding loops of both C2 domains into the bilayer, with somewhat higher preference to the bilayer containing t-SNAREs and this partitioning could be further augmented by the addition of PIP2. However, Synaptotagmin maintains its position on the SNARE complex during the whole process. Recent data has shown that Complexin arrests fusion by blocking the complete assembly of SNAREpins in adjacent complexes i.e. a trans-clamping interaction. Our results suggest a simple, one-step physical mechanism by which Synaptotagmin could trigger the reversal of the trans-Complexin clamp and activate fusion, in response to Calcium.

2545-Pos Board B564
Calcium Triggered Membrane Penetration of Synaptotagmin may Provide the Driving Force to Reverse the Complexin Clamp
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Synaptic proteins, Complexin and Synaptotagmin act in sync to achieve the speed and the accuracy of the synaptic transmission. Complexin (CPX) arrests the SNARE assembly in the late stages promoting the docking of the synaptic vesicles at the active zone and along with Synaptotagmin, the calcium sensor, synchronizes the fusion of these vesicles with the influx of calcium ions following the nerve impulse. Recently, we obtained the first X-ray crystal structure representing the clamped state of SNAREpin at the docked vesicles, which shows that Complexin arrests fusion by blocking the complete assembly of the v-SNAREs in the adjacent SNARE complex. This trans- interaction generates an unusual zigzag array of half-zippered (pre-fusion) SNARE complexes between the two bilayers. Here we present experiments using a novel Nanodisc-based system that mimics a vesicle-bilayer junction that suggests